REMARKS

Claims 31-44 are currently pending in this application.

Applicants gratefully acknowledge the Examiner's kind consideration and assistance in the personal interview held at the United States Patent and Trademark Office on May 8, 2002. In compliance with 37 C.F.R. §§ 1.2 and 1.133, a written summary of the reasons warranting favorable action given orally by Applicants' representative at the interview is set forth in this Amendment and analyzed further in the responses to the rejections of record.

The amendment to the Specification reflects the current status of the parent applications to this divisional application. Support for the claim amendments defining stringency conditions in Claims 41-44 is found at page 19, lines 7-20 of the Specification.

No new matter is incorporated by this Amendment.

Interview Summary

On May 8, 2002, Applicants' Representative (hereinafter "Applicants") engaged Primary Examiner John Ulm in a personal interview regarding all pending issues in the outstanding Office Action. At the outset, Applicants pointed out that the asserted utility in the Specification, that HPTK6 was a marker for cancer in liver tissue, was specific, substantial and credible. Examiner Ulm suggested that the claimed invention was an "orphan receptor" and therefore relevant to the heightened scrutiny described in Example 12 of the Revised Interim Utility Guidelines. Applicants did not agree to this characterization and again pointed out the asserted utility was to a cancer marker, based on the presence of the protein in certain cells, and not the action of the protein in the membrane.

Some discussion followed regarding the data in Applicants' Specification that supported the asserted utilities as a marker for cancer. Applicants pointed out that the article of record (Jones et al., [*Cancer Genetics and Cytogenetics* 117: 153-158 (2000)]) cited by the Examiner in support of the utility rejection, was not probative as to the production of HPTK6 in MCF-7 cells. Examiner Ulm responded that other articles could have been cited, to which Applicants quickly pointed out that these were not of record and followed with the point that Jones does not address Applicants' data with respect to utility as a marker for liver cancer. Examiner Ulm conceded to this point.

Examiner Ulm expressed his preference for more data regarding other cell lines to reinforce the credibility of the cancer marker utility. Applicants responded that this was not necessary in light of the ample evidence of record in the Specification and that the requirement for further evidence along this line was burdensome, cumulative and undue.

Discussion then turned to the rejections under 35 USC § 102(a) and the evidence of record in the Declaration under 37 CFR § 1.131. Examiner Ulm agreed that the showing regarding the HPTK6 sequence already of record predated both the Johnson and Di Marco references, but argued that some showing of utility, and when such utility was discovered, was also required. Applicants pointed out that this was a Declaration in an *Ex Parte* proceeding not an Interference, and accordingly, no showing of utility was required by Applicants, given the lack of asserted utility in the references applied under 35 U.S.C. § 102(a).

Examiner Ulm did not agree, and conveyed his position that at least the Johnson reference disclosed a utility and hence, any Declaration under 37 CFR § 1.131 would also require a showing regarding the date of discovered utility with respect to HPTK6. Applicants responded that neither Johnson or Di Marco disclosed any express assertion of utility, whatsoever, and

hence would not have any utility under the Revised Interim Utility Guidelines. Examiner Ulm refined his position that he believed the Northern blot data in Johnson with regard to cancer cells would mean the same to one of ordinary skill in the art as the data in Applicants' specification.

Applicants pointed out that this was not the case and that Johnson and Di Marco are both limited to characterizing the sequences they disclose, and that the conjecture of some cellular role the protein may play in these references does not amount to an asserted utility, either express or implied.

Examiner Ulm suggested analyzing the cell lines in Johnson as to predictability in the same way he had analyzed the MSF-7 cells in his last response relying on Jones. Applicants did not agree that this was, or would be, probative to finding any utility in Johnson.

Quite to the contrary, Applicants asserted that Johnson supported the credibility of the asserted utility in Applicants' Specification because the data in Johnson shows that an independent cancerous liver cell line contains HPTK6. However, this mere disclosure, in itself did not support a finding of utility in the Johnson reference as that disclosure, by itself, and unlike Applicants' Specification, expresses no asserted utility, and there is no data or analysis in Johnson to support a conclusion that HPTK6 would have any utility as a cancer marker.

Examiner Ulm did not agree with Applicants'characterization of Johnson, but Examiner Ulm did support the general proposition that alternative ways for addressing these issues were available. He stated that if it was established that Johnson (and Di Marco) had no disclosed utility, that the evidence of record under 37 CFR § 1.131 was sufficient to overcome the rejections under 35 U.S.C. § 102(a).

Discussion of the hybridization claims rejected under 35 U.S.C. 102(b) followed. Examiner Ulm stated that unless the hybridization conditions were defined within the claim itself, that under low enough stringency, binding can occur among almost any polynucleotide

pair. Applicants pointed out the low degree of similarity between the murine DNA in the Klein reference and the claimed polynucleotides. Applicants also pointed out that specific hybridization conditions could be drawn from the Specification.

When the conditions in the Specification exemplifying hybridization stringency were pointed out to Examiner Ulm, he agreed that a relatively high amount of formamide was contained in the denaturing composition. Some discussion of the general classes of proteins and what degree of stringency would be required hybridize among them followed. Examiner Ulm remarked that there would not be serious doubt that the stringency conditions discussed at page 19 of the Specification would distinguish the claimed polynucleotides from those in Klein.

Rejection under 35 U.S.C. §101

Claims 31-44 are rejected under 35 U.S.C. § 101 as purportedly lacking supporting disclosure of a specific, substantial and credible utility in the Specification. The Office Action looks to the teaching of Jones et al., [*Cancer Genetics and Cytogenetics* 117: 153-158 (2000)] in support of the rejection.

Applicants respectfully traverse. In addition to other asserted utilities, the Specification expressly asserts a specific, substantial and credible utility of HPTK6 as marker for cancer. Also, the position maintained with respect Jones et al. is not well grounded. Applicants respectfully aver that no *prima facie* case of a lack of utility has been established according to the Revised Interim Utility Guidelines, and that reliance on Jones is an improper application of the "credibility" analysis according to the Guidelines.

An express asserted utility is found on page 97, at lines 18-19 of the Specification where reference is made to the results in Table 3 showing positive indication HPTK6 for liver carcinoma and that the results indicate that HPTK6 plays a role in cancer formation of certain

cells. This asserted utility is specific, substantial and credible. The asserted utility and supporting testing is perfectly demonstrated in that healthy liver tissue is tested as a baseline and compared with cancerous liver cells showing a positive result for HPTK6.

In Figure 10, healthy liver tissue from both an adult and a fetus are tested for the presence of HPTK6. There being no detectable HPTK6 in healthy liver tissue, this forms a qualitative baseline to test for the presence of HPTK6 in cancerous liver cells. As summarized in Table 3, cancerous liver cells (Hep 3B) tested positive for HPTK6.

Despite this express assertion and supporting tests, the Office Action takes the position that the claimed invention has no credible, specific, and substantial utility in the identification of liver cancer. The Office Action maintains this position despite the utility described and tested as shown in Figure 10 [showing a baseline of zero HPTK6 in both healthy adult and healthy fetal liver tissue] and at pages 94-97 of the Specification, wherein the qualitative expression of HPTK6 mRNA in liver tissue and a cell lines representative of liver carcinoma (Hep 3B cell line) are demonstrated. The expression of HPTK6 mRNA in liver carcinoma is recorded as positive in Table 3, while, as noted at page 95, lines 30-31 (referring to Figure 10) no expression of HPTK6 mRNA is recorded for healthy liver cells.

In maintaining this position, the Office Action relies upon Jones et al., [*Cancer Genetics and Cytogenetics* 117: 153-158 (2000)] as purportedly providing evidence to rebut an assertion of utility with respect to diagnosis of breast cancer by the detection of HPTK6 mRNA over-expression in an MCF-7 cell line from Table 3. Applicants respectfully assert that this reliance on Jones et al. is not well placed.

First, Jones does not address the expression of HPTK6 in liver cells. Second, in relying upon Jones, the Office Action sets forth broad statements concerning MCF-7 cells. However,

Jones has no data or reference with respect to HPTK6 specifically. Therefore, Jones cannot be relied upon as presenting evidence reasonably relevant to HPTK6 specifically. In support of this reasoning, Applicants provide a Declaration under 37 C.F.R. § 1.132 signed by Dr. Paul J. Godowski, and enclosed with this Amendment as Attachment A.

Applicants point out that the Examiner's reliance on the Jones reference, in traverse to Applicants' assertion of credible utility, is overly burdensome. The Office Action mailed March 7, 2002, at pages 2-3, states as follows:

> "One of ordinary skill in the art, however, would not accept these results as supporting a conclusion that the expression of HPTKA6 mRNA in a liver of [sic] breast sample is diagnostic for cancer simply because cell lines are not necessarily representative of the cancers from which they were derived. To illustrate this fact, the Jones et al. publication (Cancer Genetics and Cytogenetics 117: 153-158, 2000) is being cited because it shows that different MCF-7 cell stocks are known to not even be predictive of one another."

This is an improper application of the "credibility" analysis according to the Revised Interim Utility Guidelines. Applicants set forth in their previous response that there is a substantial, credible, and specific utility for HPTK6, namely the detection and treatment of liver cancer by HPTK6 by using HPTK6 antibodies, antisense, etc. This utility is expressly asserted in at page 97 of the Specification. According to the Revised Interim Utility Guidelines, an assertion is credible unless the logic underlying the assertion is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

There is no reasonable basis to doubt that the results in Table 3 of the Specification logically support Applicants' assertions above. In addition, the Revised Interim Utility Guidelines Training Materials published at www.uspto.gov state specifically, on page 5, with respect to the credibility analysis that "nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. *Therefore, the credibility of such an assertion would*

not be questioned" (*emphasis* added). Therefore, the burden placed on Applicants in response to their asserted utility of HPTK6 as a cancer marker is improper as prescribed by the Revised Interim Utility Guidelines for rejections under 35 U.S.C § 101 at the United States Patent and Trademark Office.

Applicants asserted utility also survives the remaining analysis in that the claimed polynucleotides can serve as diagnostic markers for the specific disease of liver cancer, and that identification or diagnosis liver cancer is a substantial "real world" application. Applicants note that there has been no substantial written analysis in any previous Office Action with respect to the utility of detecting cancer in liver cells. This asserted utility and supporting testing is fully demonstrated in that healthy liver is tested as a baseline and compared with cancerous liver cells showing a positive result for the presence of HPTK6. In Figure 10, healthy liver tissue from both an adult and fetus are tested for the presence of HPTK6. There being no detectable HPTK6 in healthy liver tissue, this forms a baseline for testing the presence of HPTK6 in cancerous liver cells. As summarized in Table 3, cancerous liver cells (Hep 3B) cells tested positive for HPTK6. It is possible that the Examiner may criticize the finding that the HEP 3B are a cell line, in the same way that the MCF-7 cell line was critically reviewed in the previous Office Action. In anticipation of such criticism, Applicants refer to Figure 2 in Johnson et al. already of record (and addressed more fully below as it has been applied under 35 U.S.C. § 102(a)). In Figure 2 of Johnson, in lane k, human HepG2 cells (another line of cancerous liver cells) also tested positive for the presence of HPTK6. This confirms, by external validation, the asserted utility in Applicants specification as a marker for cancerous liver cells.

Applicants respectfully summarize that they have expressed an asserted utility in their Specification with respect to HPTK6 as being a marker for cancer of the liver. Two baseline

measurements from separate liver tissue samples have established that HPTK6 is not detectable in healthy liver cells. In the specification, a cancerous liver cell line (HEP 3B) provides a positive result for HPTK6. This result is confirmed, by external and independent evaluation, for another line of cancerous liver cells (Hep G2) in Johnson. Therefore, the asserted utility is clearly demonstrated as credible and further scrutiny or criticism is unjustified.

Applicants respectfully submit that the present disclosure provides a specific, substantial and credible utility for the claimed invention. Accordingly, reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §101 is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31-44 are under 35 U.S.C. §112, first paragraph as failing to adequately teach how to use the instant invention for the reasons given in the rejection of record under 35 U.S.C. §101. Applicants respectfully traverse.

A deficiency under 35 U.S.C. §101 also creates a deficiency under 35 U.S.C. §112, first paragraph. In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967). Thus, in order to be enabled, a claim must be supported by a disclosure showing practical utility. As discussed above, the present disclosure provides a specific, substantial and credible utility for the claimed invention. Thus, the claimed invention meets the requirements of 35 U.S.C. §112, first paragraph.

Reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §102(a)

Claims 31-44 are rejected under 35 U.S.C. §102(a) as being anticipated by Johnson et al. (PNAS 90:5677-5681, Jun. 1993). Additionally, Claims 31-33, 35-38, and 40-44 are rejected

under 35 U.S.C. §102(a) as being anticipated by Di Marco (J. Biol. Chem. 268:24290-24295, 15 Nov. 1993).

With respect to both Johnson and Di Marco, the Office Action has taken the position that the current evidence of record is insufficient to swear behind the references because the current evidence does not address Applicants' discovery date of utility. Under In re Moore, 444 F.2d 572 (CCPA 1971) it was clearly established that in *Ex Parte* prosecution, unlike Interference practice, no showing of utility is required in a Rule 1.131 Declaration unless the reference to be overcome also discloses a utility. This proposition has been upheld in later cases such as In re Borkowski, 505 F.2d 713 (CCPA 1974).

The Office Action has taken the position that the Johnson and Di Marco references disclose a utility. Applicants strongly traverse this characterization in that neither Johnson or Di Marco survive any fair analysis as having a specific, substantial and credible utility under the Revised Interim Utility Guidelines. Furthermore, it would be inconsistent to maintain that either Johnson or Di Marco disclose any utility under the Guidelines, and reject Applicants Specification as lacking a disclosed utility as a marker for identifying liver cancer.

Prior to the time of the invention, the HTPK6 protein had no well-established utility. Neither Johnson nor Di Marco disclose any expressed assertion of a specific and substantial utility as required under the Guidelines. In any reasonable application of the Revised Interim Utility Guidelines, an application with a claim based on the disclosure in either of these references would be rejected under 35 U.S.C. § 101 as not disclosing any specific or substantial utility and that credibility would not even be assessed. Nevertheless, assuming *in arguendo*, that some specific and substantial utility had been asserted, neither reference would withstand the credibility analysis.

In the above-mentioned Personal Interview, Examiner Ulm expressed his contention that the disclosure of Johnson was the same or equivalent to Applicants' Specification in disclosing an "implied" utility based on the Northern Blot data in Johnson indicating the presence of HPTK6 in certain carcinoma cells. This is not the case. Johnson simply discloses that HPTK6 is found in certain cancerous cell lines, but never states or provides comparative evidence that HPTK6 would serve as a marker for cancer. This can be compared with the rigorous comparison done between healthy liver tissue and a cancerous liver carcinoma in Applicants' Specification. Only Applicants demonstrate a tissue specific comparative study. In addition, Applicants' Specification expressly states that HPTK6 can be a marker for cancer.

Given the degree of distinction between Johnson and the Specification, it should be evident that they are not equivalent. Assuming *in arguendo,* that the analysis in the previous Office Action is correct with regard to predictability in immortal cell lines, there can be no implied utility in Johnson. And even if this critical analysis on cell line predictability has some reasonable basis, there is no evidence to support a logical conclusion that HPTK6 is a cancer marker as Johnson merely states that HPTK6 is found in carcinoma cell lines. Given this alone, HPTK6 could be found in any cell line, cancerous and non-cancerous.

Di Marco falls even further from the mark. Di Marco is limited to characterizing the protein and conjectures as to its role as a receptor for Nerve Growth Factor. There is no asserted utility, and no comparative evidence that could even be construed to imply a utility. In addition, given that Di Marco is concerned with speculating on the receptor role of HPTK6, the disclosure would be subject to the more rigorous analysis of receptor-based utilities called for in Example 12 of the Revised Interim Utility Guidelines. This is not the analysis to which Applicants utility assertion would be subjected as a cancer marker utility is much more easily found credible than a receptor utility.

As demonstrated above, no specific, substantial and credible utility is disclosed in either Johnson or Di Marco. Accordingly, Applicants cannot be required to show discovery of utility in their 1.131 Declaration as evidence in overcoming these references. The evidence of record is sufficient to overcome both these rejections. See In re Moore, 444 F.2d 572 (CCPA 1971); In re Borkowski, 505 F.2d 713 (CCPA 1974). Applicants request full and favorable consideration of Declaration under 35 U.S.C. §1.131 filed on May 1, 2000.

In view of the above, Applicants submit that the claimed invention has been established as invented prior to the publication of either Johnson or Di Marco. Reconsideration and withdrawal is respectfully requested.

Rejection under 35 U.S.C. §102(b)

Claims 41-44 are rejected under 35 U.S.C. §102(b) as being anticipated by Klein et al. (EMBO J. 8(12):3701-3709, 1989).

The Examiner asserted that "because any oligo will bind to any nucleic acid under the appropriate conditions, these claims encompass any oligonucleotide." The Examiner also asserted that "since all nucleic acid molecules will bind (hybridize) to one another under certain conditions the oligonucleotide which was employed in Figure 1 of Klein et al. would certainly bind to the nucleic acid molecule of any of Claims 41-44 under the appropriate conditions.

Applicants respectfully traverse this rejection as overcome by the amendment to claims 41-44. Applicants note that the Examiner is using the sequence of a mouse trkb (i.e., Figure 1) to obviate a human sequence as in the present invention. Claims 41-44 claim an isolated nucleic acid that will hybridize under those conditions expressly described in the specification on page 19, lines 7-18. Although non-homologous nucleic acids will hybridize under non-stringent conditions, only homologous nucleic acids will hybridize under the now claimed stringent conditions.

In the previously submitted sequence alignments, it has been shown that SEQ ID NO: 7 has an 18.68% homology with mouse trkb and SEQ ID NO: 3 has a 43.98% homology with mouse trkb, and both sequence alignments have many gaps in which there is no homology at all. These factors indicate a very poor case for hybridization of mouse trkb with SEQ ID NO: 7 and SEQ ID NO: 3 under stringent conditions. Thus, there would be no appreciable binding of trkb to the nucleic acid of the present invention, which requires stringent conditions for hybridization. Accordingly, the mouse trkb sequence of Klein et al. is not sufficiently homologous to the nucleic acid sequences claimed in the present invention, and cannot support a rejection under §102, as either expressly or inherently disclosed.

Reconsideration and withdrawal of all the rejections is respectfully requested.

CONCLUSION

In light of the above, this application is now in condition for allowance and Applicants request favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER, RUDNICK LLP

July 30, 2002
Date

Steven B. Kelber
Registration No: 30,073
Attorney of Record

Patrick R. Delaney
Registration No: 45,338

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone: (202) 861-3900
Facsimile : (202) 223-2085

SERIAL NO. 09/236,939

DOCKET NO.: 9491-018-27X DIV

MARKED-UP COPY OF PARAGRAPHS, AS AMENDED

On page 1, lines 11-14, the paragraph there has been amended as follows:

This is a divisional application of U.S. Serial No. [08/170,557] 08/170,558, filed on December 20, 1993, now U.S. Patent No. 6,001,621, which is a continuing application of U.S. Serial No. 08/157,563, filed November 23, 1993, now abandoned, to which applications priority is claimed under 35 U.S.C. §120.

SERIAL NO. 09/236,939

DOCKET NO.: 9491-018-27X DIV

MARKED-UP COPY OF THE CLAIMS

41. (Twice Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule encoding amino acid sequence SEQ ID NO:8 and complements thereof, wherein said hybridization occurs at (A) an ionic strength of 0.015 M NaCl/0.0015 M sodium citrate/0.1 sodium dodecylsulfate and temperature 50° C for washing; employing during hybridization as a denaturing agent 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42 °C; or (B) 50% formamide, 5xSSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5xDenhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecylsulfate, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 0.2xSSC and 0.1% sodium dodecylsulfate.

42. (Twice Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:7 and complements thereof, wherein said hybridization occurs at (A) an ionic strength of 0.015 M NaCl/0.0015 M sodium citrate/0.1 sodium dodecylsulfate and temperature 50° C for washing; employing during hybridization as a denaturing agent 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42 °C; or (B) 50% formamide, 5xSSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5xDenhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecylsulfate, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 0.2xSSC and 0.1% sodium dodecylsulfate.

43. (Twice Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule encoding amino acid sequence SEQ ID NO:4 and complements thereof, wherein said hybridization occurs at (A) an ionic strength of 0.015 M NaCl/0.0015 M sodium citrate/0.1 sodium dodecylsulfate and temperature 50° C for washing; employing during hybridization as a denaturing agent 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42 °C; or (B) 50% formamide, 5xSSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5xDenhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecylsulfate, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 0.2xSSC and 0.1% sodium dodecylsulfate.

44. (Twice Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:3 and complements thereof, wherein said hybridization occurs at (A) an ionic strength of 0.015 M NaCl/0.0015 M sodium citrate/0.1 sodium dodecylsulfate and temperature 50° C for washing; employing during hybridization as a denaturing agent 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42 °C; or (B) 50% formamide, 5xSSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5xDenhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecylsulfate, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 0.2xSSC and 0.1% sodium dodecylsulfate.